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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,671	08/01/2001	C. Frank Bennett	RTS-0297	7102

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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NH 08053

EXAMINER
MCGARRY, SEAN

ART UNIT	PAPER NUMBER
1635	6

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09-920671 ~~09/920,671~~	Applicant(s) TUCKER, DARREN F.
	Examiner Sean R McGarry	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of an antisense compound that targets a nucleic acid encoding CoREST (defined by SEQ ID NO: 11) in Paper No. 4 is acknowledged. The traversal is on the ground(s) that the individual antisense oligonucleotides recited in claim 3 are not novel and unobvious over each other. This is not found persuasive because applicant has only made a statement of disagreement without providing arguments or evidence that the antisense are obvious over each other. Applicant has not specifically addressed the reasons for restriction set forth in the restriction mailed 12/5/02. It is noted that applicant has elected to pursue a generic claim drawn to CoREST defined by SEQ ID NO: 11. The restriction of the specific antisense set forth for claim 3 is now moot since this claim has been canceled.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to antisense based therapies for the treatment/prevention of diseases or conditions that are associated with CoREST via antisense compounds targeted to a CoREST encoding nucleic acid defined by SEQ ID NO:11. The instant specification provides examples that show inhibition of CoREST in cells in culture.

These Examples do not show what affect the inhibition had on cell phenotype, for example. The Examples appear only to show that CoREST expression was inhibited. One in the art is not provided with any evidence from these examples that would show by correlation the treatment of any particular disease, for example.

The specification provides a review of prior art that indicates what biological activity CoREST has but this review does not provide any guidance for any disease that is directly treatable by the inhibition of CoREST, for example. Although CoREST appears to be associated with biological pathways that may be associated with disease in general, there has been no specific guidance what diseases in particular may be treatable in any predictable manner with antisense oligonucleotide inhibition of CoREST, for example.

The range of diseases contemplated for treatment includes hyperproliferative diseases including cancer and neuronal cancer, and developmental disorders. The range of conditions embraced in vast. The amount of guidance for any particular condition or disease is very small. One in the art would not know, based on the specification as filed, how to trea such a vast array of diseases where these diseases have various and unrelated pathologies (e.g. different tissues or organs are effected, rates of progression are different, and different stages of development may be affected) where the specification provide no specific guidance for one in the art to rely upon in devising a treatment where a general treatment plan clearly would not be adequate for such a vast range of conditions, especially in an art that is unpredictable.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are

searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to

ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

For those reasons above it is clear that one in the art would be required to perform undue trial; and error experimentation to practice the invention as claimed. The quantity of undue experimentation would include the determination of what specific diseases may be treated with antisense to CoREST and devise a course of treatment that overcomes the obstacles as exemplified in the references above, for example.

Claims 1, 2, and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andres [PNAS Vol. 96:9873-9878, cited by applicant] and Bennett et al [US 5,988,148], Baracchini et al [US 5,801,154], Weintraub et al [Scientific American, January 1990, pages 40-46], and applicant admission on page 40.

The claimed invention is an antisense compound targeted to a nucleic acid encoding CoREST (defined by SEQ ID NO: 3). The invention also includes limitations where the compound is an antisense oligonucleotide which have various recited modifications and where the antisense compounds are included in various carriers and a method of inhibiting of CoREST in cells.

Andres et al have taught that together REST and CoREST mediate repressionof the Type Iisodium chanelpromoter in neuronal cells and also that CoREST/REST complex may mediate long term repression essential to maintenance of cell identity. It is asserted at page 9877 that "[t]he details of the mechanism by which REST represses its target genes are not known.[I]t is possible that CoREST interacts and interferes with components of the basal transcriptional apparatus. [a]lternatively, CoREST could function as a repressor by recruiting, either directly or indirectly, histone deacylase activity (citations omitted). [t]he corepressors NcoR/SMRTe apparently repressthrough both mechanisms (citations omitted). [I]n this regard, it will be interesting to determine whether CoREST is independent of the NcoR/SMRTe pathway." It is clear from the passage, for example, that the art provides a clear motivation to perform further study of

the properties of CoREST. Andres et al do not teach the use of antisense oligonucleotides to inhibit CoREST.

Baracchini et al have taught, at column 6 for example, that antisense oligonucleotides can be used for research purposes and have also taught, at column 6, that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 4 it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

Bennett et al have taught general targeting guidelines at columns 3-4, for example. It has been taught to target 5'untranslated regions, start codons, coding regions, and 3'untranslated regions of a desired target, for example. It has been taught in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics, for example. At column 5 it has been taught that antisense

oligonucleotides 8-30 nucleotides in length are particularly preferred. At columns 6-7 it has been taught preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, for example. At columns 7-8 it has been taught that preferred antisense oligonucleotides comprise modified sugar moieties including2'-O-methoxyethyl. It has also been taught to modify nucleobases in antisense oligonucleotides at column 8-9 which includes the teaching of 5-methyl cytosine and at column 10 it has been taught chimeric antisense oligonucleotides. All of the above referred to modification are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. At columns 10-24, for example it has been taught numerous "carriers" for antisense oligonucleotides. In table I it has been taught the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification).

Weintraub has taught that one in the art can use antisense oligonucleotides to elicit information about a given genes function.

At page 40 of the instant specification it is admitted that the antisense of the invention were designed based on the published sequence of CoREST referenced as GenBank AI922671 (SEQ ID NO:11).

It would have been obvious to make antisense oligonucleotides as claimed since the prior art has asserted that there is more information that needs to be learned about CoREST function. The prior art has also taught that antisense oligonucleotide are versatile tools for the elucidation of gene function and that antisense can be designed

based on a known sequence with a reasonable expectation of success. Furthermore the art has taught various modification and carriers for antisense oligonucleotides that all provide advantages for their use in cell, for example. The art has therefore provided a clear motivation to make the invention as claimed.

The invention as a whole would therefore *prima facie* obvious to one in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM
March 6, 2003

SEAN McGARRY
PRIMARY EXAMINER